PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2004/002437	30.07.2004	31.07.2003

International Patent Classification (IPC) or both national classification and IPC
C07D223/16

Applicant
RANBAXY LABORATORIES LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IB2004/002437

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 41 (as regards industrial applicability)

because:

☒ the said international application, or the said claims Nos. 41 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	6, 7, 11, 14-36
	No:	Claims	1-5, 8-10, 12, 13, 37-41
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-41
Industrial applicability (IA)	Yes:	Claims	1-40
	No:	Claims	

2. Citations and explanations

see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/IB2004/002437

Re Item III.

The present **claim 41** relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT.
Consequently, no opinion will be formulated with respect to industrial applicability of the subject-matter of this claim.

[For the assessment of the aforesaid claim on the question whether it is industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but will allow, however, claims to a (known) *compound for* first *use in medical treatment* and the *use* of such a compound *for the manufacture of a medicament* for a new medical treatment.]

Re Item V.

The following documents (D) are considered to be relevant:

D1: ..... US-A-4692522 (8 September 1987);
D2: ..... US-A-4575503 (11 March 1986);
D3: ..... Database WPI, Section Ch, Week 198011, Derwent Publications Ltd., London, GB; &
JP-A-55/015418 (2 February 1980);
D4: ..... WO-A-02/076375 (3 October 2002);
D5: ..... HOUBEN-WEYL: "Methoden der Organischen Chemie", vol. V/2b: "Arene und Arine", GEORG THIEME VERLAG, STUTTGART, 1981, pages 282-284;

1. NOVELTY (Article 33(2) PCT):

The present application does not satisfy the criterion set forth in Article 33(2) PCT because the subject-matter of **claims 1-5, 8-10, 12, 13** and **37-41** is not new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT):

The document **D1** discloses (cf., column 22, example 2B) a process for the preparation of 3-Amino-1-(t-butoxycarbonylmethyl)-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one which comprises the hydrogenation (*hydrogen gas*) of 3-Azido-1-(t-butoxycarbonyl-methyl)-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one in *ethanol* at *room temperature* and in the presence of a *palladium on carbon* catalyst.
Furthermore **D1** teaches (cf., column 38, example 23) the preparation of the 3(S)-enantiomer of 3-Amino-1-(t-butoxycarbonylmethyl)-2,3,4,5-tetrahydro-1H-[1]benz-azepin-2-one by *chiral resolution* with L-tartaric acid.

As a result of the wording of the present claims 1 "...containing **up to** 8% of 7-bromo-3-azido t-butyl ester..." (which does not exclude the use of *pure* 3-Azido-1-(t-butoxy-carbonylmethyl)-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one) and 5 "...wherein a **source of hydrogen gas** is used..." (which does not exclude the use of *hydrogen gas*), the document **D1** has to be considered to be novelty-destroying with respect to the present process **claims 1-5, 8-10, 12** and **13**.

The document **D2** also discloses (cf., column 49, lines 25-26) a process for the preparation of 3-Amino-1-(t-butoxycarbonylmethyl)-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one which comprises the hydrogenation (*hydrogen gas*) of 3-Azido-1-(t-butoxycarbonyl-methyl)-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one in *ethanol* at *room temperature* and in the presence of a *palladium on carbon* catalyst.
For same reasons as given above, **D2** is considered to be novelty-destroying with respect to the present process **claims 1-5, 8-10** and **12**.

As the *degree of purity* of a chemical compound cannot constitute a "new element" imparting novelty to a claimed compound (see, for example, the decision **T 990/96** of the European Board of Appeal), it is further considered that the documents **D1**, **D2** and **D4** (see, the 3 / 3(S) -Amino-1-(t-butoxycarbonylmethyl)-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one of the examples 2B and 23 of **D1**; the 3-Amino-1-(t-butoxy-carbonylmethyl)-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one and the (3S)-1-(carboxymethyl)-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-1H-

[1]benzazepin-2-one hydrochloride of the examples 23 and 27 of **D2**; and the (3S)-1-(carboxymethyl)-[[(1S)-1-(ethoxy-carbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one hydrochloride of the examples 1 and 2 of **D4**) are prejudicial to the novelty of the present compound **claims 37** (**D1** and **D2**) and **38** (**D2** and **D4**) and the present process / composition / method **claims 39-41** (**D2** and **D4**).

The present dependent process **claims 6**, **7** and **11** are novel over **D1** and **D2** on account of (the use of) (i) the source of hydrogen, which is selected from "...*ammonium formate*, *formic acid* and *alkali metal formate* or *mixtures* thereof..." and (ii) the organic solvent selected from *formic acid* or *acetic acid*.

The present process **claims 14-21** are novel over **D1** and **D2** because of the *two hydrogenation steps* a) (with Raney nickel) and b) (with a noble metal catalyst).

The prior art **D1** does not disclose the synthesis of *benazepril*,
the document **D2** does not disclose the use of a *trifluoromethane sulphonic ester* of the present formula III in the preparation of benazepril, and
the document **D4** does not disclose the preparation of *3(S)-Amino-1-(t-butoxycarbonyl-methyl)-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one* (via a (double) hydrogenation of the 3-azido t-butyl ester of the present formula IV).
The present process **claims 22-36** are therefore novel over **D1** and **D2**.

The documents **D3** and **D5** do not relate to the preparation of *3(S)-Amino-1-(t-butoxycarbonyl-methyl)-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one* or *benazepril*.

2. INVENTIVE STEP (Article 33(3) PCT):

The present application does not satisfy the criterion set forth in Article 33(3) PCT because the subject-matter of **claims 1-41** - as far as it is novel (see, item 1 above) - does not appear to involve an inventive step (Rule 65(1)(2) PCT):

2.1. the process according to the present **claims 1-13**:

Document **D1** - which represents the **closest prior art** - teaches (cf., column 22, example 2B) a process for the preparation of 3-Amino-1-(t-butoxycarbonylmethyl)-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one which comprises the hydrogenation (*hydrogen gas*) of 3-Azido-1-(t-butoxycarbonyl-methyl)-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one in *ethanol* at *room temperature* and in the presence of a *palladium on carbon* catalyst.
Furthermore **D1** teaches (cf., column 38, example 23) the preparation of the 3(S)-enantiomer of 3-Amino-1-(t-butoxycarbonylmethyl)-2,3,4,5-tetrahydro-1H-[1]benz-azepin-2-one by *chiral resolution* with L-tartaric acid.

The process of present **claim 1** - as far as it is novel (see, item 1 above) - **differs** from the aforesaid **D1** process merely in that the starting material of the present formula IV, i.e. the compound 3-Azido-1-(t-butoxy-carbonylmethyl)-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one ***contains*** as an impurity the compound 3-Azido-***7-bromo***-1-(t-butoxy-carbonylmethyl)-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one.

In the light of the prior art **D1** the **problem** to be solved by the process of the present claim 1 resides in the provision of a process for the preparation of 3-Amino-1-(t-butoxycarbonylmethyl)-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one using 3-Azido-1-(t-butoxy-carbonylmethyl)-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one ***containing*** as an impurity the compound 3-Azido-*7-bromo*-1-(t-butoxy-carbonylmethyl)-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one as a starting material.

This problem has been **solved** by the (novel) process according to the present **claim 1** (cf., the present examples 1 and 2).

This solution (as far as it is novel) cannot, however, be considered to involve an inventive step for the following reasons:

1. The person skilled in the art being confronted with the aforesaid problem would have started from the known process of the closest prior art **D1**.
2. In the course of this investigation he would have found that - while applying the teaching of the example 2B of **D1** (the reaction conditions of the example 2B of **D1** (hydrogenation with H_2 / *10% Present description/C*) *are* ***identical*** *with* the process features of the present claims 1-5, 8-10, 12 and 13 !) to the present 3-Azido-1-(t-butoxy-

carbonyl-methyl)-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one ***containing*** 3-Azido-*7-bromo*-1-(t-butoxy-carbonylmethyl)-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one as an impurity - the reduction of the 3-azido group *goes along with* the dehalo-hydrogenation of the 7-bromo group.

3. It is therefore considered that the person skilled in the art would have solved the present problem by simply following the teaching of example 2B of **D1**.

Accordingly, the process of the present **claim 1** has to be regarded to be obvious in the light of the prior art **D1**.

Dependent **claims 2-13** do not appear to contain any features which, in combination with the features of claim 1 to which they refer, meet the requirements of the PCT in respect of inventive step (the process features of the present claims 2-5, 8-10, 12 and 13 are known from **D1**, and the features of the present claims 6, 7 and 11 (the use of *alkali metal formate* as a source of hydrogen, and the use of *formic/acetic acid* as a solvent) merely represent conventional modifications of the hydrogenation process of **D1** well known to the person skilled in the art).

2.2. the process according to the present **claims 14-21**:

Again, document **D1** is considered to represent the **closest prior art**.

The process of present **claim 14 differs** from the process of **D1** (example 2B) in that
(i) the compound 3-Azido-1-(t-butoxy-carbonylmethyl)-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one (containing up to 8% of the compound 3-Azido-***7-bromo***-1-(t-butoxy-carbonylmethyl)-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one) is hydrogenated in the presence of ***Raney nickel*** (cf., the present step a)), and that
(ii) the so obtained 3-Amino-1-(t-butoxy-carbonylmethyl)-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one (containing up to 8% of the compound 3-Amino-***7-bromo***-1-(t-butoxy-carbonylmethyl)-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one) is hydrogenated in the presence of a noble metal catalyst (cf., the present step b))

In the light of the prior art **D1** the **problem** to be solved by the process of the present claim 1 resides in the provision of a process for the preparation of 3-Amino-1-(t-butoxycarbonylmethyl)-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one using 3-Azido-1-(t-

butoxy-carbonylmethyl)-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one (***containing*** as an impurity the compound 3-Azido-*7-bromo*-1-(t-butoxy-carbonylmethyl)-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one) as a starting material.

This problem has been **solved** by the process according to the present **claim 14** (cf., the present example 3).

This solution cannot, however, be considered to involve an inventive step for the following reasons:

It is known from **D2** (cf., example 1; column 31, lines 17 - 35; and column 32, lines 1-16) that the 3-azido group of 3-Azido-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-ones may be reduced with *either* Raney Ni *or* Palladium on carbon as a catalyst.
It is further known (cf., for example, **D3** (page 105, scheme 2 of JP-A-55/015418) or **D5**) that Palladium (on carbon) is a suitable catalyst for the dehalo-hydrogenation of aromatic halides.
It is would therefore appear that - in the absence of any surprising or unexpected effect - the process according to the present independent process **claim 14** has to be regarded to be obvious in the light of the prior art **D1** - **D3**.

Again, the dependent process **claims 15-19** do not appear to contain any features which, in combination with the features of claim 14 to which they refer, meet the requirements of the PCT in respect of inventive step (the process features of the present claims 15-17 and 19-21 are known from **D1/D2**, and the present claim 18 (the use of *formic/acetic acid* as a solvent) merely concerns a conventional modification of the hydrogenation process of **D2**).

2.3. the process according to the present **claims 22-36**:

The document **D4** is considered to represent the **closest prior art**.
D4 discloses (cf., claim 5 and the examples) a process for the preparation of benazepril hydrochloride which comprises the condensation of 3-Amino-1-(t-butoxycarbonyl-methyl)-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one with trifluoromethane sulphonic ester of ethyl (R)-2-hydroxy-4-phenylbutyrate in the presence of an organic solvent (such as methylene chloride) and a base (such as N-methyl morpholine).

The process of present **claim 22 differs** from the process of **D4** only in that the starting material 3(S)-Amino-1-(t-butoxy-carbonylmethyl)-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one is prepared by a process according to steps a)-c) of the present claim 22.

In the light of the prior art **D4** the **problem** to be solved by the process of the present claim 1 resides in the provision of a further process for the preparation of benazepril.

This problem has been **solved** by the process according to the present **claim 22** (cf., the present example 5).

This solution cannot, however, be considered to involve an inventive step for the following reasons:

1. The synthesis steps a) - c) of the present claim 22 are, in fact, *identical* with the process steps as detailed in the examples 2B and 23 of the prior art **D1** ((i) the present step b) is not performed if the metal catalyst in step a) is a noble metal catalyst as defined in the present claim 24 (cf., the present claim 25), and (ii) the process steps a) and b) do not require the presence of the 3-(Azido or Amino)-*7-bromo*-1-(t-butoxy-carbonylmethyl)-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one as an impurity (cf., the present steps a) and b): "...***optionally*** containing up to 8% of *7-bromo*...")).
As the person skilled in the art would have contemplated the use of the 3(S)-Amino-1-(t-butoxy-carbonylmethyl)-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one of the example 23 of **D1** in the process according to **D4** it is considered that the process of the present **claim 22** is obvious in the light of **D4** and **D1**.

2. If the impurity 3-(Azido or Amino)-*7-bromo*-1-(t-butoxy-carbonylmethyl)-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one is present, claim 22 represents a process claim which is dependent from the present process claim 1 and / or 14.
As the independent process claims 1 and 14 cannot be considered to involve an inventive step for the reasons given above (see, items 2.1 and 2.2) it is considered that - in the absence of any surprising or unexpected effect - the process according to the present independent process **claim 22** has to be regarded to be obvious in the light of the prior art **D4** on the one hand and **D1** - **D3** on the other hand.

Again, the dependent process **claims 23-36** do not appear to contain any features which, in combination with the features of claim 22 to which they refer, meet the requirements of the PCT in respect of inventive step.

3. INDUSTRIAL APPLICABILITY (Article 33(4) PCT):

The subject-matter of the present **claims 1-40** concerns chemical processes, chemical compounds and pharmaceutical compositions and is therefore considered to be industrial applicable in the sense of Article 33(4) PCT.

4. MISCELLANEOUS:

4.1. The present claims 32 and 33 contain a reference to the description (cf., the "intermediate compound VI"). According to Rule 6.2(a) PCT, claims should not contain such references except where absolutely necessary, which is not the case here.

4.2. On page 2 of the present description, the document **D4** should have been cited by its application number WO-A-02/076375.

4.3 For the sake of clarity the expression "metal catalyst" on page 5, line 17 of the present description should have been replaced by "noble metal catalyst" (Article 6 PCT: clarity)